REMARKS/ARGUMENTS

I. THE CLAIMED INVENTION

The presently claimed invention is directed towards methods of detecting the presence of one or more allele-specific anti-MHC antibodies in a sample. The methods comprise contacting the sample with one or more recombinant MHC molecules, each of which binds specifically a different allele-specific anti-MHC antibody. The allele-specific anti-MHC antibodies are antibodies that are specific for a naturally occurring MHC allele.

II. THE OFFICE ACTION OF MARCH 3, 2006

A. WRITTEN DESCRIPTION

The Office Action of March 3, 2006 rejected pending claims 1-7, 9-17, 20 and 22-28 under 35 U.S.C. §112, first paragraph because the claims allegedly "contain[] subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), a the time the application was filed, had possession of the claimed invention." *Office Action of March 3, 2006,* page 2.

The Office Action asserts that "[c]laims 1-7, 9-17, 20 and 22-28 are drawn to recombinant MHC molecule that binds only one antibody, ..." *Office Action of March 3, 2006,* page 2. Applicants respectfully disagree with this characterization of the presently claimed invention. The presently claimed invention is drawn towards methods of detecting anti-MHC antibodies in a sample using recombinant MHC molecules, but is not directed to the recombinant MHC molecules themselves. In other words, the present claims do not claim recombinant MHC molecules *per se*, but instead they claim methods of using these recombinant MHC molecules to detect anti-MHC antibodies. The difference between a claim directed towards recombinant MHC molecules and a claim directed towards the use of recombinant MHC molecules is not trivial.

The Office Action relies heavily upon Federal Circuit precedent (*Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1216 (Fed. Cir. 2002)) to support its position that "the specification does not describe recombinant MHC molecules in a manner that satisfies either the Lilly or the Enzo standards." *Office Action of March 3, 2006,* page 4.

Applicants assert that the cited cases are inapplicable to the pending application. First, in each of the cases the Office Action cites, the claims at issue were directed towards novel DNA or protein molecules themselves, or involved methods using novel DNA sequences, rather than methods involving known proteins. In each of the cited cases, the claims were directed to novel DNA or protein molecules, where the identity of the molecule was *unknown* prior to the filing date of the patents at issue. For example, in *Lilly*, the claims were directed to human insulin cDNA, although human insulin DNA had never been characterized.

The cases upon which the Office Action relies are inapplicable to the pending application, because, unlike the facts behind the cited cases, the pending claims are not directed towards novel DNA or proteins, or methods of using novel DNA or proteins. And, more importantly, none of the cases upon which the Office Action relies imposes the duty of reanalysis of molecules whose structures are already known and part of the state of the art. The Federal Circuit has addressed the written description requirement in the context of biotechnological patents, where the claims simply utilize biological materials that are not new or unknown. In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003), the claims at issue were directed to types of cells that could be used to produce human EPO, and the court stated that "[the] Eli Lilly [decision] … [is] inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." *Amgen v. Hoechst* at 1332. The court then stated that the challengers to the Amgen-owned patent at issue "can only challenge the adequacy of the disclosure of the … host cell – not the human DNA itself." *Id.* Similar to the facts in *Amgen v. Hoechst,* the claims here are not directed towards DNA or proteins themselves, and the claim terms here do not utilize

"new or unknown biological materials that the ordinarily skilled artisan would easily miscomprehend." Rather, the claims of the pending application are directed towards methods of detecting anti-MHC antibodies using recombinant MHC molecules. The sufficiency of the disclosure in supporting the currently pending claims, therefore, must be analyzed in light of "methods of detecting anti-MHC antibodies," rather than the MHC molecules themselves, the characteristics of which were known as of the filing date of the present application. Applicants assert that, when viewed in the proper context, the specification fully describes the claimed subject matter as it relates to methods of detecting anti-MHC antibodies.

Even more relevant to the presently claimed invention, the Federal Circuit, in overturning a decision by the Board of Patent Appeals and Interferences ("the Board"), recently clarified the written description requirement in the context of claims that utilize known biological materials in *Capon et al. v. Eshhar et al. v. Dudas,* 418 F.3d 1349 (Fed. Cir., 2005). Specifically, *Capon* clarifies the written description requirement as delineated by *Eli Lilly* and *Enzo,* among others.

In *Capon*, the claims involved in the interference were directed to a chimeric gene, which "combines segments of DNA in a way that does not occur in nature." *Capon* at 1351. The DNA components of the chimeric genes were "*known* antigen-binding-domain producing DNA and *known* lymphocyte-receptor-protein producing DNA." *Capon* at 1351 (emphasis added). The Board, however, held that "neither party's specification provides the requisite description of the full scope of the chimeric DNA or encoded proteins...." *Capon* at 1354. In support of their decision, the Board cited *Eli Lilly, Enzo* and other cases as controlling precedent. But in challenging the Board's decisions, the Appellants asserted that the "requirement that the specification must reproduce the 'structure, formula, chemical name, or physical properties' of [the] DNA combinations had been *overtaken by the state of the science.*" *Capon* at 1356 (emphasis added).

In discussing the current state of the written description requirement under 35 U.S.C. §112, first paragraph, the Federal Circuit stated that "[s]ince the law is applied to each invention *in view of the state of relevant knowledge*, [the] application [of the written description

requirement] will vary with differences in the state of knowledge in the field ...." *Capon* at 1357 (emphasis added). In reviewing and overturning the Board's decision, the Federal Circuit held that "[t]he Board erred in refusing to consider the state of scientific knowledge...." *Capon* at 1357. Furthermore, the Federal Circuit stated that the Board's reliance on *Eli Lilly, Enzo* and the other "written description cases" for the case at bar was incorrect and explained that "[n]one of the cases to which the Board attributes the requirement of total DNA re-analysis, *i.e., Regents v. Lilly, Fiers v. Revel, Amgen* [*v. Chugai*], or *Enzo Biochem*, require a re-description of what was already known." *Capon* at 1357. The Federal Circuit elaborated that "[t]he Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization." *Capon* at 1358. It is particularly noteworthy that the Federal Circuit made this assertion that nucleotide sequences need not be fully presented to satisfy the written description requirement, because the sequences of a sufficient number of sequences of the DNA chimera components were available in the published literature and methods were known and provided for linking the components of the chimera. *Capon* at 1355-1356.

Thus, the Federal Circuit not only clarified the requirements for written description in the context of known biological materials, but also reiterated that a proper written description analysis must take into account "the state of scientific knowledge." Similar to the facts surrounding *Capon*, representative numbers of allele-specific MHC molecules that can be utilized in the claimed methods were delineated well before the filing of the present application and claims. Indeed, Table 4 lists multiple alleles of HLA (MHC) and their loci. The specification also points the reader to websites that depict the coding sequences of MHC molecules. Thus, the MHC molecules themselves were part of "the state of scientific knowledge" at the time of filing the application. The use of recombinant MHC molecules, however, for detecting anti-MHC antibodies was, to applicants' knowledge, never disclosed or even suggested in the art prior to the filing of the present application.

Accordingly, Applicants believe that the present specification adequately and sufficiently describes the presently claimed subject matter, in view of the state of the art at the time the application was filed. Reconsideration and withdrawal of this rejection are earnestly solicited.

B. ENABLEMENT

The Office Action of March 3, 2006 rejected pending claims 1-7, 9-17, 20 and 22-28 under 35 U.S.C. §112, first paragraph because the specification allegedly "does not enable any person skilled in the art to which us pertains, or with which it is most nearly connected to makes the invention commensurate in scope with these [pending] claims." *Office Action of March 3, 2006,* page 6.

In making the rejections, the Office Action states that "the specification provides no information as to structures common to … any and all recombinant MHC molecules based on structure/function correlation." *Office Action of March 3, 2006,* page 7. Further the Office Action relies on paragraph 0026 of the currently pending published application as support for its allegations that the specification fails to enable the claimed invention. Finally, the Office Action concludes that "[g]iven the above, it appears that Applicant is suggesting random experimentation in order to find the recombinant MHC molecules that will function as claimed. Random experimentation is undue." *Office Action of March 3, 2006,* page 7. Applicants respectfully disagree that "random experimentation is undue" and that such no bright line test exists when determining enablement. Rather, [t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988).

As the Office Action points out, three of the "*Wands* factors" that must be considered when determining if a specification enables the claims it supports include (a) the state of the art at the time of filing the application, (b) the amount of direction or guidance presented in the application, and (c) the breadth of the claims. Applicants assert that when at least these factors

for this application are viewed under a reasonable standard, the specification enables the full scope of the claimed invention.

It should be reiterated that the claims do not recite functionally equivalent derivatives or fragments of MHC molecules. Indeed, the Office Actions of April 11, 2003 and March 11, 2004, rejected the then pending claims under 35 U.S.C. §112, first paragraph, because the specification allegedly failed to enable the full scope of the then pending claims that included the limitation of using "recombinant MHC molecules or functionally equivalent recombinant variants, derivatives or fragments thereof." In response, Applicants amended the then pending claims to remove the phrase "or functionally equivalent recombinant variants, derivatives or fragments thereof" in relation to the recombinant MHC molecules. The enablement rejection was subsequently withdrawn, indicating the specification was deemed to enable the full scope of the claimed invention.

The Office Action's reliance on paragraph 0026 is therefore misplaced and taken out of context, because the cited passage in the Office Action describes "functionally equivalent variants, derivatives or fragments" of MHC molecules. Indeed, just three sentences after the portion of the specification that the Office Action cites, the application states in paragraph 0027 that "functionally equivalent variants, derivatives or fragments refer to MHC molecules wherein the amino acid sequence of one of more components of said MHC molecules …has been modified by single or multiple amino acid … substitution, addition and/or deletion but which nonetheless retains functional activity." And has been established above, the pending claims do not contain these limitations including functionally equivalent variants, derivatives or fragments of recombinant MHC molecules.

Thus, while the specification contemplates and describes functionally equivalent MHC molecules, the present claims do not recite such a limitation. And as has been pointed out, a proper enablement analysis requires consideration of the breadth of the claims. Applicants assert that the specification fully enables the scope of recombinant MHC molecules as the claims currently read.

When the proper breadth of claims is taken into account, Applicants assert that the specification provides adequate guidance to make and use the full scope of the claimed invention, in light of the state of the art at the time of filing the application. Indeed, paragraph 0075 of the published application outlines a strategy for preparing recombinant HLA molecules comprising, for example, removing the cytosolic tail and transmembrane domains of the HLA heavy chain and inserting the construct into a commercially available prokaryotic expression system. It should also be noted that the Examples include a description of how to make and use recombinant molecules MA-A11 and MA-B7, as well as those recombinant MHC molecules that the Office Action indicates are enabled (HLA-A2 and HLA-B8, *see Office Action of March 3, 2006,* page 6). Thus the application contains at least 4 working examples of recombinant MHC molecules that can be used to detect anti-MHC antibodies. These working examples of at least 4 recombinant MHC molecules, however, should not limit the scope of the claims solely to constructs comprising these 4 recombinant MHC molecules.

Instead, Applicants assert that, given the state of the art at the time of filing, one of skill in the art could use the teachings of the present specification to prepare additional recombinant MHC molecules. The specification is replete with listings of other HLA alleles, *e.g.,* Table 4, that could be used to generate recombinant MHC molecules. In addition, the specification directs the reader to various references and web sites that disclose nucleic acid sequences for MHC alleles. Applicants assert therefore, that, given the state of the art at the time of filing the application, one of skill in the art could apply the teachings of the working examples for HLA-A2, MA-A11, MA-B7 and HLA-B8 of the present application towards other allele specific MHC molecules to prepare myriad recombinant allele specific MHC molecules.

When viewed in the context of proper claim scope and the state of the art at the time of filing, Applicants assert that the application provides ample guidance to one of skill in the art to generate recombinant MHC molecules for their use in the claimed methods of detecting anti-MHC antibodies. Reconsideration and withdrawal of the enablement rejection is earnestly solicited.

CONCLUSION

No claims have been amended or introduced in this paper. Applicants have traversed the remaining outstanding grounds for rejection in the present application. Reconsideration and withdrawal of the outstanding rejections is earnestly solicited.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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